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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,302	06/25/2003	Danilo Porro	2027.594096/RFE	4661

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EXAMINER
SCHLAPKOHL, WALTER

ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/606,302	PORRO ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	MDL

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-33 and 35* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10 and 12-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 12/19/2006 in which claims 21-24 were amended and claim 34 was cancelled. Claims 1-10, 12-33 and 35 are pending. Claims 1-6 and 35 are withdrawn. Claims 7-10 and 12-33 are under examination in the instant Office action.

Allowable Subject Matter

The indicated allowability of claims 7-9, 12-19 and 28-33 is withdrawn in view of the newly discovered reference(s) and in view of further search and consideration by Examiner. Rejections based on the newly cited reference(s) follow.

Specification

The amendment filed 12/19/2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant has introduced headings into the "tables" originally present on pages 27-28 of the specification such that the tables now indicate the nature of materials and

methods used in the cloning of the AGD, LDGH, ALO, ARA, and RGLO enzymes. For example, while the specification previously made clear that "[i]nserts were cloned using the pYX series" of vector (page 27, line 22), and while the specification also listed vectors pYX042, pYX022, pL AGD, pH LGDH and pL ALO (page 27, bottom), it was not previously disclosed that pYX042 was cut with EcoRI to insert the AGD-1 sequence from pSTB AGD-1 thereby resulting in the making of the pL AGD expression plasmid. Furthermore, while the specification indicated that *S. cerevisiae* GRF18U were transformed with AGD; ALO; LGDH; AGD and LDGH; ALO and LDGH; and ARA and ALO (see, e.g., the table on page 30), the specification did not previously disclose the strains listed in the newly added table.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 21-23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which Applicant regards as the invention is WITHDRAWN in view of Applicant's amendment.

Claim 7, and therefore dependent claims 8-10 & 12-33, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. **These is a new rejection which was not necessitated by Applicant's amendment.**

Claim 7 recites "[a] method of generating ascorbic acid, comprising:

a) obtaining a recombinant yeast capable of converting an ascorbic acid precursor into ascorbic acid, wherein the yeast is functionally transformed with a coding region encoding a first enzyme selected from D-arabinose dehydrogenase (ARA), D-arainono-1,4-lactone oxidase (ALO), or L-gulono-1,4-lactone oxidase (RGLO),

b) culturing the recombinant yeast in a medium comprising an ascorbic acid precursor, thereby forming ascorbic acid, and

c) isolating the ascorbic acid in lines 1-8 (emphasis added). Claim 7 is vague and indefinite in that the metes and bounds of "L-gulono-1,4-lactone oxidase (RGLO)" are unclear.

Does Applicant intend an L-gulono-1,4-lactone oxidase as defined on page 19, lines 19-21, of the specification, i.e. any protein that catalyzes the oxidation of L-gulono-1,4-lactone to L-xylo-hexulonolactone which spontaneously isomerizes to L-ascorbic acid; or does Applicant intend RGLO which, as abbreviated, indicates L-gulono-1,4-lactone oxidase from *R. norvegicus* (see page 23, line 26 of the specification)?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 and 12-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection not necessitated by Applicant's amendment.**

Note: for purposes of this rejection only, RGLO has been interpreted by the Examiner to encompass any L-gulono-1,4-

lactone oxidase, not just that from *Rattus norvegicus* as the acronym would seem to indicate.

Claims 7-10 and 12-33 are drawn to methods comprising the use of recombinant yeast which have been functionally transformed with with coding regions encoding a set of D-arabinose dehydrogenase (ARA), D-arabinono-1,4-lactone oxidase (ALO), or L-gulono-1,4-lactone oxidase (RGLO) enzymes. Claims 12-13 are further limited to such enzymes wherein the ARA enzyme has at least about 70% similarity or identity with SEQ ID NO:20; the ALO enzyme has at least about 70% similarity or identity with SEQ ID NO:5 or SEQ ID NO:7; and the RGLO enzyme has at least about 70% similarity or identity with SEQ ID NO:9. Claim 14 is further limited to such a method wherein the coding region encoding the ARA enzyme has at least about 70% identity with SEQ ID NO:21; the coding region encoding the ALO enzyme has at least about 70% identity with SEQ ID NO:6 or SEQ ID NO:8; or the coding region encoding the RGLO enzyme has at least about 70% identity with SEQ ID NO:10. Thus, the claims comprise a set of coding regions/amino acids defined by the function of the encoded protein, i.e. the ability of the enzyme to confer the ability of the yeast to convert an ascorbic acid precursor into ascorbic acid. It is further noted that claims 20-26 have been included within this rejection as the claims are drawn to

embodiments which are not supported by the specification or the prior art. For example, neither the specification nor the prior art teach an RGLO enzyme from *A. thaliana*. Furthermore, claim 21 does not distinguish whether the first ALO, ARA or RGLO enzyme(s) need be derived from the organisms recited therein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification discloses two nucleic acid sequences and two protein sequences for ALO which have been isolated from *Saccharomyces cerevisiae* (see page 19, lines 10-15; claims 12-14; and SEQ ID NOS: 5-8 of the sequence listing). The specification further discloses the use of one ARA nucleic acid sequence and one RGLO nucleic acid sequence, along with their corresponding amino acid products, in such a method (see, e.g., page 25, Table at top of page; as well as SEQ ID NOS: 20-21 and 9-10). No description is provided of any other ALO, ARA, or RGLO sequences that result in a functionally transformed yeast cell capable of converting an ascorbic acid precursor into ascorbic acid. Neither is any

description provided of any structure or sequence motifs that such ALO, ARA or RGLO sequences would share. It is not even clear from the specification what the differences between the two disclosed ALO sequences are.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of at most two ALO enzymes and one ARA enzyme from one source (*S. cerevisiae*), and one rat GLO enzyme. The results are not necessarily predictive of any other ALO, ARA or RGLO sequence. Thus, it is impossible for one to extrapolate from the nucleic acids and amino acid sequences described herein those sequences that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of ALO, ARA or RGLO enzymes with even 95% or 98% similarity or identity. An article published after the effective filing date of the instant application describes ALOs only from two species: *S. cerevisiae* and *Candida albicans* (Sauer M. et al. *Applied and Environmental Microbiology* **70**(10):6086-6091, 2004; cited previously). Thus the prior art seems only to identify one additional ALO enzyme to those described in the specification.

ALO from *S. cerevisiae* was characterized by Huh, et al in 1998 as a purified enzyme from mitochondrial fractions with a molecular weight of about 60 kD (*Molecular Microbiology* **30**(4):895-903, 1998; IDS Ref. C2; see entire document, especially page 895, the Abstract). Huh et al further teach that the ALO enzyme from *S. cerevisiae* has an FAD binding domain at amino acid residues 23-56 and a transmembrane domain between at residues 172-188 (see page 897, 1st column, 1st and 2nd full paragraphs). Otherwise, no other domains, motifs or sequences responsible for ALO specific function were known at the time of Applicant's filing.

With regard to RGLO, Nishikimi et al teach the isolation of RGLO from rat and from guinea pig and note that the guinea pig homologue of rat L-gulono-1,4-lactone oxidase is a nonfunctional mutant (*The Journal of Biological Chemistry* **267**(3):21967-21972, 1992; see entire document, especially page 21967, the Abstract and page 21970, Figure 3). Nishikimi et al further teach that when the amino acid coding regions of the rat GLO gene were compared with those of the corresponding amino-acid coding regions of the guinea pig, there was 79% amino acid homology (see page 21971, 1st column, 1st full paragraph). At the nucleic acid level, the homology was 83% (ibid).

With regard to ARA, in a reference published in 1998, Kim et al teach the first cloning of an ARA enzyme from *S. cerevisiae* and note that *S. cerevisiae* ARA has homology to amino acid residues 5-14 of *C. albicans* ARA (*Biochimica et Biophysica Acta* **1429**:29-39, 1998; IDS Ref. C20; see entire document, especially pages 35-37). Kim et al further teach that ARA has structural properties that clearly place it within the aldo-keto reductase (AKR) family of proteins (see page 37). However, Kim et al also teach that *S. cerevisiae* D-arabinose dehydrogenase is the first heterodimeric protein of the AKR family. More importantly, Kim et al, as well as the rest of the prior art at the time of Applicant's filing, are silent with regard to the motifs/sequence responsible distinguishing ARA from other AKR family proteins, including its ability to convert ascorbic acid precursors to L-ascorbic acid.

Given the very large genus of sequences encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to their common sequence motifs/structures, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of ALO, ARA or RGLO sequences with 70% identity and/or similarity with SEQ ID NOS:

5-10 and 20-21. In the case of RGLO the literature shows that homology of as much as 79% at the amino acid level and 83% at the nucleic acid level is not sufficient to predict function (see above). Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those embodiments that satisfy the functional limitations of the claimed genus of ALO, ARA or RGLO enzymes with regard to their capability to convert ascorbic acid precursors into ascorbic acid as *S. cerevisiae* ALO, *S. cerevisiae* ARA and *R. norvegicus* RGLO do. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 7-10 and 12-33.

The rejection of claims 20 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter) is hereby WITHDRAWN in view of Applicant's argument (claim 20) and in view of Applicant's cancellation of the claim (claim 34).

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record set forth in the Office action mailed 8/22/2006.**

Response to Arguments

Applicant argues that Applicant's amendment to the specification lists the strains deposited, their place of deposit and their compliance with the requirements of 37 C.F.R. 1.801-1.809. Applicant further argues that *K. lactis* PM6-7A was known to the public from work published by Wesolowski et al, *Yeast* **8**:711 (1992). Applicant further argues that copies of the deposit receipts for the deposited strains and the ATCC catalog pages for the previously publicly available strains have been attached for the Examiner's convenience. Therefore, Applicant argues, the basis for the rejection has been removed.

Applicant's arguments have been carefully considered but have respectfully been found unpersuasive. Applicant's amendment does not include a complete list of strains deposited, their place of deposit and their compliance with the requirements of 37 C.F.R. 1.801-1.809. Specifically, Applicant has failed to provide such information for the *K. lactis* PM6-7A

strain. Nor does Applicant's amendment provide a sufficient description for each strain. Most importantly, Applicant has not included a statement that all restrictions on access to the biological deposits will be removed on grant of the patent in accordance with CFR 1.808 as set forth in MPEP 2410.01:

> Consequently, the mere indication that a deposit has been made under conditions prescribed by the Budapest Treaty would satisfy all conditions of these regulations except the requirement that all restrictions on access be removed on grant of the patent. *Ex parte Hildebrand,* 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

This requirement was clearly set forth on page 7 of the previous Office action:

> 'If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:
> a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;
> b) all restrictions upon availability to the public will be irrevocably removed upon the granting of the patent;
> c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request for the enforceable life of the patent, whichever is longer;

d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and
e) the deposit will be replaced if it should ever become inviable.

Failure to make one of the preceding indications in response to this Office Action will result in the rejection being maintained in either a further Non-Final or a Final rejection.'

Finally, as has already been explained above, the amendment to the specification includes new matter.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Receipt is acknowledged of the terminal disclaimer filed 12/19/2006. The rejection of claims 24-27 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-15 of U.S. Patent No. 6,630,330 is WITHDRAWN in view of Applicant's submission of an effective terminal disclaimer.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claim 34 under 35 U.S.C. 102(b) as being anticipated by Roland et al (WO 85/0175; of record) is WITHDRAWN in view of Applicant's cancellation of the claim.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the

Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic

Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

March 8, 2007

DAVID GUZO
PRIMARY EXAMINER